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Landes Highlights

RNA editing helps to fine-tune potassium channel

Mary Y. Ryan, Rachel Maloney, Jeffrey D. Fineberg, Robert A. Reenan and Richard Horn

RNA editing is a molecular process through which some cells can make discrete changes to specific nucleotide sequences during transcription. The enzyme adenosine deaminase acting on RNA (ADAR) binds to specific double-stranded pre-mRNA structures and deaminates particular adenosine (A) nucleotides to inosines (I). Inosines are then read as guanosines by the translation machinery. In some cases such a single-base change may lead to an alteration of RNA stability, or an aminoacid change that can have consequences such as the creation of an alternative splice site or a change in protein function. RNA editing events have been reported for various protein types, including voltage-gated and ligand-gated ion channels. In a recent study, Dr Richard Horn and co-workers showed that RNA editing at four sites in *eag*, a *Drosophila* voltage-gated potassium channel, results in the substitution of amino acids into the final protein product that are not encoded by the genome. In particular, editing resulted in the following changes: K467R (site 1, top of the S6 segment), Y548C, N567D and K699R (site 2-4, within the C-terminal domain). The authors mutated these residues individually and expressed the channels in *Xenopus* oocytes. A fully edited construct (all four sites) has the slowest activation kinetics and a paucity of inactivation, whereas the fully unedited channel exhibits the fastest activation and most dramatic inactivation. Editing at site 1 was shown to inhibit steady-state inactivation. Moreover, channels edited at site 1 are more sensitive to changes in extracellular Mg^{+2} than unedited channels. Taken together, the study results show that even a minor change in amino acid side-chain chemistry and size can have a dramatic impact on channel biophysics, and that RNA editing is important for fine-tuning the channel's function.

www.landesbioscience.com/journals/20/article/22314/

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Channels

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LANDES BIOSCIENCE

MiR-93 promotes tumor angiogenesis and metastasis via LATS2 suppression

Ling Fang, William W. Du, Weining Yang, Zina Jeyapalan Rutnam, Chun Peng, Haoran Li, Yunxia Q. O'Malley, Ryan W. Askeland, Sonia Sugg, Mingyao Liu, Tanvi Mehta, Zhaoqun Deng and Burton B. Yang

MicroRNAs (miRs) have diverse regulatory functions in cell activities associated with cell proliferation, differentiation, invasion, tumor formation, angiogenesis and metastasis. The largest functional group of miRs are the ones involved in cancer development. Recently, Dr Burton Yang and colleagues reported that miR-93 is significantly upregulated in human breast carcinoma tissues. The researchers stably expressed miR-93 in a human breast carcinoma cell line (MT-1) and found that tumors formed by the miR-93 cells contain more blood vessels than those formed by the control cells. Co-culture experiments indicated that the MT-1 cells display a high activity of adhesion with endothelial cells and can form larger and more tube-like structures with endothelial cells. Lung metastasis assays were performed in a mouse metastatic model, and miR-93 expression was found to promote tumor cell metastasis to lung tissue. In cell culture, expression of miR-93 enhanced cell survival and invasion. The authors looked for the potential target that mediated miR-93's effects and identified the large tumor suppressor, homology 2 (LATS2). Higher levels of LATS2 were associated with cell death in the tumor mass. Silencing LATS2 expression promoted cell survival, tube formation and invasion, while ectopic expression of LATS2 decreased cell survival and invasion. The study findings show that miR-93 promotes tumor angiogenesis and metastasis by suppressing LATS2 expression. Therefore, inhibition of *miR-93* function may be a feasible approach to repress tumor metastasis.

http://www.landesbioscience.com/journals/cc/article/22670/

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CellCycle

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LANDES BIOSCIENCE

Imprinted small RNAs and their contribution to human disease

Michael Girardot, Jérôme Cavaillé and Robert Feil

More than a hundred protein-coding genes are controlled by genomic imprinting in humans. These atypical genes are organized in chromosomal domains, each of which is controlled by a differentially methylated "imprinting control region" (ICR). At several imprinted domains, this epigenetic mechanism involves the action of long non-coding RNAs. It is less well appreciated that imprinted gene domains also transcribe hundreds of microRNA (miR) and small nucleolar RNA genes. This striking phenomenon is the focus of a recent review by Dr Robert Feil and colleagues. Almost seven percent of the known miRs are encoded by imprinted domains and nowhere in the genome there is such a high density of small regulatory RNAs as at imprinted domains. The evolutionary reasons for this remarkable enrichment of small regulatory RNAs at imprinted domains remain unclear. However, recent studies show that imprinted small RNAs modulate specific functions in development and metabolism and also are frequently perturbed in cancer. This review summarizes the current understanding of imprinted small RNAs in the human genome and discusses how perturbation of their expression contributes to disease.

www.landesbioscience.com/journals/epigenetics/article/22884/

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epigenetics

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Epigenetic marks in hESC at
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Complex impact of HDAC expression in CLL clinical course (p. 1403)

LANDES BIOSCIENCE

Mediator MED23 regulates basal transcription via P-TEFb interaction

Wei Wang, Xiao Yao, Yan Huang, Xiangming Hu, Runzhong Liu, Dongming Hou, Ruichuan Chen and Gang Wang

The multi-subunit complex Mediator transduces regulatory information from transcription regulators to the RNA polymerase II (RNAP II) apparatus. Growing evidence suggests that Mediator plays roles in multiple stages of eukaryotic transcription, including elongation. A new study by Dr Gang Wang and colleagues set out to investigate the detailed mechanism by which Mediator regulates elongation. They demonstrated that Mediator MED23 subunit controls a basal level of transcription by recruiting elongation factor P-TEFb (positive transcription elongation factor), via an interation with its CDK9 (cyclin-dependent kinase 9) subunit. In particular the mRNA level of *Egr1*, a MED23-controlled model gene, was reduced 4-5 fold in *Med23*$^{-/-}$ ES cells under an unstimulated condition. However, *Med23*-deficiency did not alter the occupancies of RNAP II, GTFs (general transcription factors), Mediator complex, or transcriptional activator ELK1 at the *Egr1* promoter. Instead, *Med23* depletion resulted in a significant decrease in P-TEFb and RNAP II (Ser2P) binding at the coding region, but no changes for several other elongation regulators. ChIP-sequencing revealed that Med23-deficiency partially reduced the P-TEFb occupancy at a set of MED23-regulated gene promoters. Finally, MED23 was shown to interact with CDK9 in vivo and in vitro. In conclusion, these results provide mechanistic insight into how Mediator promotes RNAP II into transcription elongation.

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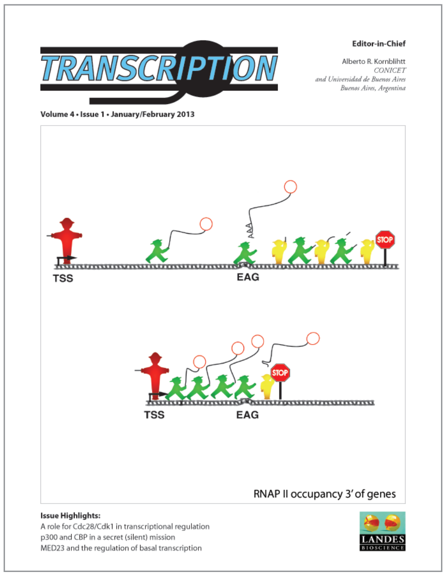

TRANSCRIPTION

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RNAP II occupancy 3' of genes

Issue Highlights:
A role for Cdc28/Cdk1 in transcriptional regulation
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